REVIEW ARTICLE

Can Drugs Cause Depression? A Review of the Evidence

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Drug-induced depressive disorders are classified in the DSM-III-R as organic mood syndrome, depressed type. The ability of certain drugs to cause depression is of clinical relevance because organic mood syndrome is a component of the differential diagnosis of depressive symptoms. Consequently, psychiatric textbooks often provide different lists of drugs thought to be capable of causing depression. Strong evidence supporting the existence of causal associations is often lacking. There is no specific drug for which there is definitive evidence of a causal association with depressive symptoms or depressive disorders. Nevertheless, for a number of drugs, the evidence is suggestive, although not conclusively, of a causal association. Despite this, rational decisions about the continuation or discontinuation of drugs can often be made. In this paper, the literature is reviewed and guidelines are suggested for the management of patients with depressive symptoms which may be related to drugs.

Key Words: depression, depressive disorder, organic mood disorder, organic mental disorder

INTRODUCTION

A large number of drugs may be capable of causing depression. Among these are many prescription drugs, non-prescription drugs and drugs of abuse. According to the DSM-III-R (American Psychiatric Association 1987), a drug-induced depression, if severe enough to resemble a major depressive episode, should be diagnosed as organic mood syndrome, depressed type. Drug-induced organic mood syndrome and other organic mood disorders are a component of the differential diagnosis of patients presenting with depressive symptoms. Many contemporary textbooks of psychiatry contain lists of drugs which are purported to cause depression (Kaplan and Sadock 1991; Stoudemire 1987; Arana and Hyman 1991). Unfortunately, there is little concordance among these lists.

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The inconsistent nature of the literature is not restricted to psychiatric reference sources, but can be identified in pharmacological sources as well. Table 1 lists assertions regarding several drugs from three pharmacological reference sources (Gilman et al 1990; Dukes 1988; Canadian Pharmaceutical Association 1991); one psychiatric reference is included in the table for comparison (Kaplan and Sadock 1991). There are areas of disagreement and consensus for many of the drugs presented in the table.

Drug-induced depression is a topic of considerable clinical importance. Both depressive disorders and depressive symptoms are common among patients in medical treatment settings (Blacker and Clare 1987; Kamerow 1988; Wells et al 1989). Depression in this context is usually regarded as having a multifactorial etiology. Clearly, medically ill patients are subjected to significant psychological and social stressors. In addition, however, medically ill patients frequently take one or more of the medications purported to cause depression. Hospitalized patients, in particular, tend to

Table 1

Drugs listed as causing depression in contemporary psychiatric and pharmacological reference sources

	Reference source			
Drug	Kaplan and Sadock 1991	Goodman and Gilman 1990	Dukes 1988	Canadian Pharmaceutical Association 1992
β-blocker (propranolol)	yes	yes	yes	yes
Corticosteroids	yes	yes	yes	yes
Digitalis	yes	no	no	no
H-2 blockers	yes	no	no	yes
Metoclopramide	yes	no	no	no
Sedative-hypnotics	yes	yes	no	yes
Methyldopa	yes	yes	yes	yes
Clonidine	yes	yes	no	no
Oral contraceptives	yes	yes	no	yes
Anabolic steroids	yes	no	yes	no
Psychostimulants	yes	yes	yes	yes
L-dopa	yes	yes	yes	yes

take a large number of medications (Nies 1990). The possibility that medications contribute to the depressive morbidity experienced by these patients is of obvious clinical concern.

Drug-induced depression is also of scientific interest. The mechanisms of action and pharmacological activities of many drugs have been described. The ability of specific drugs to cause depression may be related to the known pharmacological actions of these drugs, for example, at specific receptor sites. Knowledge of such mechanisms could help elucidate the pathophysiology of depressive disorders. It is widely believed that reserpine can cause depression, although by contemporary scientific standards, the evidence supporting an association is not as strong as is often assumed (Wildmer 1985). Based on the association between reserpine and depression, animal models and theories relating abnormalities in noradrenergic neurotransmission to clinical depressive disorders (Bunney and Davis 1965) have been developed which have contributed to the identification of many antidepressants.

This review is based upon Index Medicus and Medline searches covering the past 20 years, and a supplementary search using Psychological Abstracts, covering the past ten years. In addition, the bibliographies of the papers were examined, and additional relevant citations were identified. Drugs which have been implicated in depression by at least one publication in the past 20 years are presented in Table 2.

The purpose of this paper is to review the published studies of drug-induced depression. It will weigh the evidence for and against the existence of causal associations between specific drugs and depressive symptoms or depressive disorders. Judgements about causal relationships will be made based on the application of traditional epidemiological criteria (Hennekins and Buring 1987). These criteria are the following: the strength of the association (where a valid parameter is available that is not the result of bias in the study design or confounding with other risk factors), the biological plausibility of the association when considered within the context of neurochemical theories of depression, the consistency of the data in different studies, and the existence of a temporal relationship in which exposure to the drugs precedes the onset of depressive symptoms. An effort will be made to apply these criteria to studies of each drug, in order to reach a conclusion about the strength of evidence supporting a causal association.

Drugs which have been implicated only on the basis of one or two case reports will not be discussed. Obviously, for these drugs, there is insufficient evidence of an association, let alone a causal one. Drugs which have been reported to cause depression in more than two case reports will be reviewed, as will drugs for which empirical investigations have been published. However, where many clinical case reports have been published, the individual case reports will not be cited. Reserpine will not be discussed because it is now rarely prescribed.

Propranalol and other β-blockers

Numerous case reports have described the occurrence of depressive symptoms in patients treated with propranolol and other β-blockers. The clinical features of the reported depressive episodes resemble those of non-organic major depressive disorders (Patten and Lamarre 1992). Table 1 documents considerable agreement among reference sources that these drugs can cause depression.

Neurobiological evidence suggests that β-adrenergic receptor function may be involved in the pathophysiology of depressive disorders. For example, reduced binding of tritiated dihydroalprenolol to rat cortical tissue has been reported after long-term treatment with desipramine (Sarai 1978; Mishra et al 1979; Sellinger-Barnette et al 1980; Riva and Creese 1989; Sethy and Harris 1981; Heal et al 1989), amitriptyline (Sellinger-Barnette et al 1980; Heal et al 1989; Nelson et al 1989), doxepin (Clements-Jewery 1978), nortriptyline (Sellinger-Barnette et al 1980; Sethy and Harris 1981), clomipramine (Sellinger-Barnette et al 1980), tranylcypromine (Sellinger-Barnette et al 1980; Heal et al 1989) and electroconvulsive therapy (Bergstrom and Kallar 1979; Pandey et al 1979; Deakin et al 1981; Kellar et al 1981; Belmaker et al 1979; Kellar and Bergstrom 1983; Nimogaonkar et al 1985; Biegon and Israeli 1986). These findings seem to be consistent with reports of increased β-adrenergic receptor binding in the brains of suicide victims (Mann et al 1986; Biegon and Israeli 1988). By blocking β-adrenergic receptors, β-blockers lead to a compensatory increase in the number of β-adrenergic receptors in various tissues (Aaribs and Molinoff 1982; Glaubiger and Lefkowitz 1977; Severson et al 1986), a mechanism which has been postulated to explain the propranolol's purported ability to cause depression (Petrie et al 1982; Pollack et al 1985).

The strongest evidence of an association between β-blockers and depression is from two studies, both of which used antidepressant prescriptions as proxy markers for the existence of clinically relevant depressive disorders. One study used a cross-sectional design (Avorn et al 1986), and the other, a retrospective cohort design (Thiessen et al 1990). Both studies found an association between the prescription of antidepressants and the use of β-blockers. The retrospective cohort study reported incidence ratios of 2.1 to 4.8 (depending on the comparison group), suggesting that propranolol may be associated with a two- to four-fold increase in the incidence of depressive disorders. The retrospective cohort design allowed the researchers to conclude that exposure to β-blockers preceded prescription of the antidepressants.

These findings have been drawn into question by a recent case-control study based on a New Jersey medicaid database (Bright and Everitt 1992). This study found that patients in the database with a depression marker (an in-hospital claim listing a depression diagnosis, an ECT claim code, or a pharmacy claim listing an antidepressant) were more likely to have been exposed to β-blockers than matched controls; the odds ratio was approximately 1.5. However, when exposure to β-blockers was placed into a conditional logistic regression model which included proxy markers for several potential confounders (benzodiazepine use, number of non-psychiatric outpatient visits and number of prescriptions filled for drugs other than β-blockers), the strength of the association between depression and exposure to β-blockers diminished and was no longer statistically significant. In this analysis, benzodiazepine use was regarded as a proxy measure for "psychological symptoms," and the other two potential confounders were regarded as proxies for "illness or willingness to see a health care provider." The researchers noted that all three variables were associated with the depression markers and with the use of β-blockers. The analysis determined that, within this data set, the observed association between exposure to β-blockers and the depression markers could be explained on the basis of confounding by these variables. These findings raise the possibility that the associations found in previous studies were observed because physicians were prescribing β-blockers with greater frequency to patients who, because of some ill-defined psychological characteristic(s) or illness-associated variable(s), were more

Table 2

Drugs implicated in causing depression

Alcohol[1]
Alpha-2-adrenergic agonists (clonidine, methyldopa)[1]
Amphotericin
Anabolic steroids[1]
β-blockers (betaxolol, nadolol, propranolol, timolol)
Bismuth nitrate
Carbamazepine
Cis-retinoic acid
Corticosteroids
Cyclosporin
Digitalis[1]
Flunarizine
H-2 blockers (cimetidine, ranitidine)[1]
Levodopa
Mazindol
Methylxanthines (caffeine, theophylline)[1]
Metoclopramide
Metronidazole
Nifedipine
Organic nitrates
Phenytoin
Psychostimulants (fenfluramine, methylphenidate, pemoline, phenylpropanolamine)[1]
Reserpine
Sedative-hypnotics (barbiturates, benzodiazepines, methaqualone)[1]
Thiazide diuretics

[1]drugs for which the published evidence was judged sufficient to warrant inclusion in the review

likely to become depressed. However, these findings do not necessarily invalidate those of previous studies and may be in need of replication. In particular, this study measured ten potential confounders or response-modifying variables and, on the basis of the analysis, determined that the three variables described above were confounders. This type of determination is somewhat exploratory and requires confirmation by further studies.

Several other studies have failed to find associations between the use of β-blockers and depression. One study failed to find an association between depressive disorders (diagnosed using the Diagnostic Interview Schedule), depression rating scale symptom scores and the use of propranolol for medical outpatients (Bartels et al 1988). However, this study compared a group of patients selected because they were taking propranolol with a group of volunteers, and the possibility of selection bias makes interpretation of these results difficult. Another study found that propranolol was not associated with depressive symptoms in a clinical trial evaluating it for the treatment of anxiety (Binstock et al 1984). However, the finding cannot necessarily be generalized to the more common use of propranolol for the treatment of medical conditions, such as angina or hypertension. Another uncontrolled study failed to find an association between the dose of propranolol and depression rating scale scores (Griffin and Friedman 1986), but the lack of a control group detracts from this study. Furthermore, the lack of a dose-response relationship does not provide firm evidence that propranolol does not cause depression. For example, saturation or threshold effects could mask a dose-response relationship. For methodological reasons, these three studies cannot be regarded as strong evidence that propranolol does not cause depression.

Several additional studies have failed to find significant associations between propranolol and depressive symptoms or depressive disorders. These studies include a cross-sectional survey of cardiac patients conducted by Carney et al (1987) and prospective studies by Stoudemire et al (1984) and Schleifer et al (1991). Because of the sound methods used in these studies, the failure to find an association cannot easily be attributed to bias or to other methodological deficiencies. However, for other reasons, these studies cannot be regarded as strong evidence that propranolol does not cause depression. For example, Carney et al (1987) studied 77 subjects, 39 of whom had been exposed to propranolol and 20 of whom satisfied the DSM-III criteria for major depressive disorder. Assuming an odds ratio of 2.0, it can be estimated (Fleiss 1981) that the proportion of patients treated with propranolol in the population who would be expected to be depressed would be approximately 0.32, and the proportion of non-propranolol treated patients who would be expected to be depressed would be approximately 0.19. Using a power formula based on the binomial theorem (Rosner 1990) and a two-sided alpha value of 0.05, the study's power to detect a difference of this magnitude is estimated at 25%. Hence, the possibility of type II error cannot be excluded. However, if the odds ratio is assumed to be 4.0, as suggested by the retrospective cohort study discussed above (Thiessen et al 1990), the study would have had much more power to detect the association (approximately 71%). The study by Stoudemire et al (1984) also had low power because the sample was even smaller (11 subjects in the group treated with propranolol). The prospective study by Schleifer et al (1991) had a larger sample, but did not use the traditional design of a prospective cohort study, in which depressed individuals would generally be excluded from the exposed and non-exposed cohorts at the outset of the study. In the study by Schleifer et al, all depressed and non-depressed patients were included in the follow-up, and the existence of a depressive disorder at baseline was included in a logistic regression model (where the existence of a depressive disorder three to four months later was the dependent variable) as a covariate. More of the patients were depressed at the beginning than at the end of the follow-up period, which makes interpretation of the result — that propranolol was not a significant predictor of depression — difficult to interpret.

In summary, two large-scale studies using prescription plan data bases have found that exposure to β-blockers is associated with the prescription of antidepressants and therefore is presumably associated with the occurrence of depressive disorders. A subsequent study suggested the existence of non-causal mechanisms by which an association could occur in such studies. Many other negative studies have been published. However, these studies do not provide strong evidence of the absence of an association. The relationship is biologically plausible. Overall, the evidence appears insufficient to prove the existence of a causal relationship between propranolol and depression, but suggests that such a relationship may exist.

α-2-adrenergic agonists

The two α-2-adrenergic agonists in common clinical use are clonidine and methyldopa. These drugs can be regarded as sympatholytic, or anti-adrenergic, because they stimulate pre-synaptic α-receptors, thereby inhibiting noradrenergic neurotransmission. Clonidine acts directly at the α-2-adrenergic receptor. Methyldopa is metabolized to methylnorepinephrine, which subsequently stimulates α-2-adrenergic receptors (Gerber and Nies 1990). Soon after the introduction of methyldopa, there were reports of depression as a side-effect.

Abnormalities of alpha-adrenergic receptors have been reported in patients with depression. For example, increased platelet α-2-adrenoreceptor binding (Doyle et al 1985; Healy et al 1982/1983) and increased α-2-adrenoreceptor mediated platelet aggregation (Garcia-Sevilla et al 1983) have been reported in depressed patients. These findings seem to be consistent with the observation that long-term desipramine treatment may produce a reduction in the sensitivity of α-2-

adrenergic receptors in the brains of rats (McMillen et al 1980; Spyraki and Fibiger 1980). However, evidence that α-2-adrenoreceptors have increased sensitivity in depressed patients seems to be contradictory to the observation that the response of growth hormones to clonidine is blunted in depressed patients (Charney et al 1982; Checkley et al 1981; 1984; Mitchell et al 1988).

There is a widespread acceptance (Beers and Passman 1990) that clonidine and methyldopa can cause depression (see Table 1). However, few studies have supported the existence of an association between α-2-adrenergic drugs and depression. Four surveys of depressive symptoms in clinical populations have failed to find evidence of an association between methyldopa and depression (Bant 1978; DeMuth and Ackerman 1983; Snaith and McCoubrie 1974; Bulpitt and Dollery 1973). Clonidine has apparently never been studied. Because of small samples and the inclusion of other patients taking drugs that might cause depression in the comparison groups, it is impossible to conclude definitively from these studies that methyldopa does not cause depressive symptoms. However, there is a lack of empirical support for the existence of an association. Consideration of whether or not these drugs are causally associated with depression is premature in view of the lack of evidence that they are associated with depression at all.

Given the dissonance between the assertions of many clinical pharmacological and psychiatric reference sources and the findings regarding α-2-adrenergic agonists and depressive symptoms, further research is needed. The persistence of the belief that these drugs can cause depression (in the face of a lack of empirical support for this belief) may reflect cumulative unpublished observations of clinicians prescribing this drug.

Oral contraceptive agents

The potential existence of a relationship between oral contraceptives and depression has been acknowledged for several decades and is accepted in many clinical reference sources. As with some other drugs, potential mechanisms have been proposed whereby oral contraceptives cause depression (Wynn 1975). They involve alterations of tryptophan metabolism related to a drug-induced deficiency of vitamin B-6, which, according to the model, may be subsequently expressed as a deficiency in the synthesis of serotonin in the central nervous system. However, contemporary neurochemical theories of depression tend not to regard a deficiency of serotonin as a pathophysiological mechanism underlying depressive disorders. Nevertheless, one published clinical trial found that vitamin B-6 supplements produced an elevation in scores on the Beck Depression Inventory of depressed women who were taking oral contraceptives and who had biochemical evidence of a vitamin B-6 deficiency (Adams et al 1973).

Double-blind controlled studies have also been conducted (Goldzieher et al 1971; Leeton et al 1971; Leeton 1973), none of which has found statistical evidence of an association between oral contraceptives and depressive symptoms. However, none of them used a conventional measure of depressive symptomatology and cannot necessarily be regarded as providing definitive evidence that an association does not exist. In the Royal College of General Practitioners' Oral Contraception study, depression was one of the most common reasons for which women chose to discontinue using oral contraceptives (Kay 1984). In a recent twin study, depressed mood was also a commonly reported subjective side-effect (Kendler et al 1988). Although there is no evidence that oral contraceptives can induce a syndrome resembling major depression, depressed mood appears to be a commonly reported subjective side-effect. Given the inconsistent and negative findings, the association must be a weak one and one for which there is no evidence of a causal relationship.

Digoxin

The typical neuropsychiatric complication of digoxin therapy is delirium. However, depressive features have also been described. Nonetheless, these patients typically exhibit some evidence of cognitive impairment. A recent prospective study found the use of digoxin to be a statistically significant predictor of depressive disorders in patients discharged from hospital after a myocardial infarction (Schleifer et al 1991). The analysis used logistic regression to adjust for a number of potential confounding variables, including the severity of the physical illness. Also, more patients had depressive disorders at baseline than at the end of the follow-up period, which makes interpretation of the findings difficult. They require replication.

Sedative-hypnotic drugs and alcohol

Many clinicians believe that sedative-hypnotic drugs can cause, or aggravate, depressive symptoms. However, few studies have been conducted which support the existence of an association. A nested case-controlled study identified an association between symptoms of depression (measured by the depression subscale of the Brief Symptom Inventory) and the abuse of methaqualone (Buckner and Mandell 1990). However, methaqualone is now obsolete, and the importance of this finding is unclear. Only case reports and case series have reported depression in association with the use of benzodiazepines and benzodiazepine withdrawal. Although a large number of cross-sectional studies have found an association between alcohol and depression or depressive disorders (Powell et al 1982; Chetwynd and Pearson 1983; Deykin et al 1987; Parker et al 1987; Haack et al 1988; Backon 1990), such studies cannot establish the temporal relationship between the use of the drug and the onset of depression and hence cannot provide strong evidence of a causal association.

Psychostimulants and sympathominetics

Several case reports have described the emergence of depressive syndromes in patients withdrawing from fenfluramine, methylphenidate and pemoline. Two uncontrolled studies have also found increases in depressive symptoms after withdrawal from fenfluramine (Oswald et al 1971; Steel and Briggs 1972). However, in the DSM-III-R framework, such patients would probably be diagnosed as having amphetamine or similarly acting sympathomimetic withdrawal, rather than an organic mood disorder. Diagnostic features of amphetamine or similarly acting sympathomimetic withdrawal are depressed mood, fatigue, insomnia or hypersomnia and psychomotor agitation (American Psychiatric Association 1987).

A high prevalence rate of affective disorders has been found in clinical samples of cocaine abusers (Gawin and Kleber 1986; Weiss et al 1986). However, in some cases, cocaine may be abused in an effort to self-medicate depressive symptoms, and in some cases the depressive symptomatology may be the result of cocaine withdrawal, which would not be classified as an organic mood disorder. Only a few isolated cases have reported depressive symptoms induced by the use of psychostimulants (pemoline and phenylpropanolamine), rather than by withdrawal from these drugs.

Another psychostimulant which may be related to the occurrence of depressive symptoms is caffeine. Two cross-sectional surveys have found higher than expected depressive symptom scores among heavy caffeine users, defined in these studies as more than 750 mg/day and more than 600 mg/day, respectively (Greden et al 1978; James and Crosbie 1987). However, two other studies failed to find such an association (Winstead 1976; Mino et al 1990). The negative studies cannot be regarded as strong evidence against the existence of an association. One of these studies (Winstead 1976) looked at 135 subjects, 34 of whom were heavy caffeine users. Assuming an overall prevalence of elevated depressive symptom scores of 0.25, an odds ratio of 2.0 and a two-sided alpha value of 0.05, the power of this study to detect the association would be only 37%. In the other negative study (Mino et al 1990), a very conservative definition of heavy caffeine ingestion was used (250 mg/day). The negative findings of this study cannot be regarded as evidence that the higher levels of exposure identified in the other studies are not associated with depressive symptoms.

If the existence of an association between heavy caffeine use and depressive symptoms is accepted, the possibility that some people ingest large quantities of caffeine because they are depressed precludes the conclusion that heavy caffeine use causes depressive symptoms. For example, depressed patients may ingest large quantities of caffeine in an effort to combat pre-existing symptoms of low mood and low energy. The inability to determine the temporal relationship between exposure to high doses of caffeine and the emergence of depressive symptoms can be regarded as a general methodological limitation of the cross-sectional designs of the relevant studies.

Corticosteroids and anabolic steroids

The Boston Collaborative Drug Surveillance Program (1972) reported that 21 of 676 hospitalized patients exposed to prednisone had "acute psychiatric reactions," while only two of these patients were "profoundly depressed." Thirteen patients were described as "psychotic" and six as "maniacal". Hence, inappropriate euphoria or a manic syndrome is probably more common than depression. In all cases, the neuropsychiatric symptoms resolved when the dosage of prednisone was reduced. One survey examined the relationship between the use of alternate-day prednisone therapy and psychiatric symptom scores on the General Health Questionnaire and the Present State Examination (Cordess et al 1981). The study found that patients on alternate-day steroid regimes had lower symptom scores than patients with similar conditions (myasthenia gravis and other peripheral neuromuscular disorders) who were not on steroids. The researchers, interpreting their findings in view of the widely accepted association between the use of corticosteroids and various psychiatric syndromes, concluded that an alternate-day steroid regime may be preferable to a daily regime.

A relationship between the use of anabolic steroids and depressive symptoms is suggested by the findings of two recent surveys (Perry et al 1990; Pope and Katz 1988). One compared the prevalence of mental disorders and symptoms in a group of weightlifters using anabolic steroids with that of a group of weightlifters who had never used steroids. A higher prevalence of depressive symptoms (measured using the Symptom Checklist-90) was found in the group using anabolic steroids (Perry et al 1990). There was no difference in the prevalence of major mental disorders. However, the cross-sectional design of the study presents the previously mentioned methodological limitations. For example, weightlifters who used steroids may have had psychological differences from the group who never used steroids, even before using the drugs. An uncontrolled study reported that five of 41 body-builders and football players who used steroids developed a major depressive episode (diagnosed with the Structured Clinical Interview for the DSM-III-R) during a period of withdrawal from anabolic steroids (Pope and Katz 1988). The researchers also reported an observation that some anabolic steroid users may use human chorionic gonadotropin during withdrawal in an effort to alleviate such effects.

Levodopa

A possible association between levodopa and depression was originally suggested by case reports and the clinical observations of early clinical trials. One complication in the interpretation of these observations is the fact that

Parkinson's disease itself may cause depression. Depressive symptoms complicating Parkinson's disease have been related to the severity of the illness (Gotham et al 1986; Mayeux et al 1981) and to the severity of cognitive impairment (Mayeux et al 1981; Starkstein et al 1990). One prospective study compared the depressive morbidity (using a symptom score derived from the General Practice Research Unit Interview Schedule) experienced by Parkinson's disease patients treated with levodopa with that of a comparison group treated with anticholinergic drugs and/or amantidine (Mindham et al 1976). This study found more depressive disorders in the group treated with levodopa. However, since assignment to the treatment groups was not random, but rather was at the discretion of a neurologist, the subjects may not have been comparable at baseline. In fact, the groups treated with anticholinergic and/or amantidine had fewer physical and affective signs at the onset of treatment.

Because of the confounding effects of the severity of the illness and physical disability, existing studies do not offer strong evidence that levodopa is a cause of depression.

H-2 blockers

Two H-2 blocking drugs, cimetidine and ranitidine, are in common use for treating medical conditions. Recently, another H-2 blocker, famotidine, was introduced in Canada.

Cimetidine has been associated with the occurrence of depressive syndromes by several case reports. Apparently, no empirical studies have been conducted. However, cimetidine has been used in a large number of recent comparative clinical trials, and depression is conspicuously absent from the data on side-effects presented in these studies. There is a single clinical case report of depression associated with the use of ranitidine. One placebo-controlled study found no increase in depression rating scale scores among patients treated with ranitidine (Robins et al 1984).

CONCLUSIONS

Although a large number of agents are listed as causes of depression in some psychiatric and pharmacological reference sources, the literature supporting the existence of many of the purported etiological associations is poorly developed, or non-existent.

From an epidemiological perspective, the literature is not definitive in identifying a causative role for any specific drug in the etiology of depression. In this review, evidence has been interpreted in the context of traditional epidemiological criteria for a causal relationship, including the strength and consistency of the associations as well as the biological plausibility and temporal relationships between exposure to the drugs and the development of depressive symptoms. In light of these criteria, there is no definitive evidence that any specific drug or class of drugs causes depression.

However, there is some evidence (although not conclusive) that certain drugs, such as β-blockers, digoxin and steroids, may cause depression. For other drugs, the literature is even more inconclusive. For example, while depression is a commonly reported subjective side-effect of oral contraceptive agents, there is no evidence that these drugs can produce a syndrome which would be identified as a depressive disorder by psychiatrists. Similarly, the only analytic epidemiological study exploring the relationship between sedative-hypnotic drugs and depressive symptoms found an association between methaqualone and depressive symptoms in a drug-abusing population, and it is unclear to what extent this finding can be generalized to contemporary sedative-hypnotics (particularly when these are used clinically rather than being abused). For levodopa, the confounding influence generated by the independent association between Parkinson's disease and depression also makes interpretation of existing studies difficult. For other drugs, including psychostimulants (except in withdrawal) and H-2 blockers there is no appreciable evidence that they are associated with depression at all, let alone causally. The latter conclusion applies to a large number of drugs which were not sufficiently discussed in the literature to warrant inclusion in this review. Further epidemiological study of the associations between specific drugs and depression appears warranted.

Occasionally, review articles have commented that individuals with a history of depression, or a family history of depression, may be at greater risk of developing drug-induced depressive disorders (Beers and Passman 1990; Gangat et al 1986). In epidemiological terms, an individual or family history of depression may be a "response modifier" of the associations between specific drugs and depression. Epidemiological evidence of response modification might include a finding that the relative risk of depression associated with a drug differs across strata defined as having an individual or family history of depression. Although some studies have reported data suggestive of response modification (Mindham et al 1976), there is no substantive evidence of it in the literature.

Clinical guidelines

Clinicians will often encounter patients who are depressed and who are taking drugs. In the context of clinical practice, most psychiatrists will regard depression as being determined multifactorially, and a judgement may be required as to the role of one or more drugs. As this review has illustrated, such decisions will most often have to be made in the absence of definitive scientific information. In making these judgements, clinicians should remember that some patients may experience idiosyncratic reactions to drugs, which may not be identified as population-based associations in epidemiological research. Clinicians, therefore, cannot dismiss complaints even in the absence of explanatory data in the literature.

The ability of a drug to cause depression (or other toxicity) is only one of several considerations in deciding whether to

discontinue the use of the drug. These decisions should be made on an individual basis, weighing the clinical benefits of continuing the drug against the potential risks and toxicities. Of course, these decisions require an awareness of the efficacy and potential toxicity of alternative treatments.

Guidelines for the clinical management of patients with suspected drug-induced depression must be non-specific because of the wide range of clinical circumstances. One reasonable guideline is to ensure that the patient has undergone a thorough psychiatric and medical evaluation. A detailed clinical examination may reveal information which would help to determine whether or not a drug induced a particular patient's depressive symptoms. For example, a careful history may determine that the depressive symptoms preceded the use of the medication, or may reveal that a similar episode occurred with the use of a pharmacologically similar agent in the past.

A second guideline is that standardized measures of depressive symptoms may be useful to document the relationship of depressive symptoms to exposure to the drug. No scales have been validated that measure symptoms of an organic mood disorder. However, a scale designed to measure changes in severity of depressive symptoms (as opposed to scales designed to identify depressive disorders) and which places relatively less emphasis on physical symptoms would be a reasonable choice.

If a drug is discontinued because of the emergence of depressive symptoms and the symptoms resolve after the discontinuation of the drug, the best course of action may depend on the efficacy, side-effects and safety of the available alternatives. If the alternatives are decidedly inferior to the original drug, then a rechallenge with the original drug may be indicated for some patients. However, stopping and starting some drugs may in itself be hazardous. For example, abrupt discontinuation of clonidine may cause rebound hypertension in some patients.

In summary, the scientific evidence associating specific drugs with depression is not extensive, and some information presented in reference sources may consequently be poorly supported by research. Further research is required on clinical and scientific grounds. However, an awareness of the existing literature allows psychiatrists to make clinical judgements required in managing patients who become depressed while exposed to pharmacological agents.

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